

## **REMARKS**

### ***Status of Claims***

Claims 80-83 and 87-93 are currently pending. Claim 80 is currently amended. Claims 91-93 are added. Support for the amended and added claims is found throughout the specification as originally filed, *inter alia*, in the following: page 2, lines 6-7, Figure 11, and page 55, lines 19-21. Accordingly, Applicants submit that no new matter is introduced into the specification by way of the present amendments pursuant to 35 U.S.C. § 132. Applicants respectfully request entry of the amendments, reconsideration of the rejections, and allowance of the pending claims.

Applicants note that the amendments of the response filed January 28, 2008 have not been entered pursuant to the Advisory Action.

### ***35 U.S.C. § 103(a)***

Claims 80-83 and 87-90 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Yan *et al.* (U.S. Patent No. 5,641,749; “Yan”) in view of Milbrandt *et al.* (U.S. Patent No. 6,284,540; “Milbrandt”). Applicant respectfully request withdrawal of this rejection for the reasons provided herein.

As stated by the Supreme Court, the framework for the objective analysis for determining obviousness under 35 U.S.C. 103 is stated in *Graham v. John Deere Co.*<sup>1</sup> The factual inquiries enunciated by the Court are as follows:

- (1) Determining the scope and content of the prior art;
- (2) Ascertaining the differences between the claimed invention and the prior art; and
- (3) Resolving the level of ordinary skill in the pertinent art.<sup>2</sup>

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<sup>1</sup> 383 U.S. 1, 148 USPQ 459 (1966); reaffirmed and relied upon in KSR Int’l Co. v. Teleflex Inc., 127 S. Ct. 1727, 82 USPQ2d 1385 (2006).

Once the Graham factual inquiries are resolved, Office personnel must determine whether the claimed invention would have been obvious to one of ordinary skill in the art,<sup>3</sup> wherein “[a] person of ordinary skill in the art is also a person of ordinary creativity, not an automaton.”<sup>4</sup> “[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle.”<sup>5</sup>

In the present case, the examiner cites the references of Yan and Milbrandt, and based on the disclosures therein, concludes that “[i]t would have been obvious to one of ordinary skill in the art to substitute the use of the growth factor artemin, as taught by Milbrandt, in the method of treating glaucoma comprising the transplantation of transformed cells expressing GDNF, as taught by Yan.”<sup>6</sup>

Applicants respectfully disagree with the above conclusion. Artemin and GDNF are different proteins that possess different structure and different biological activity. Artemin is another name for Neublastin and accordingly shares 100% sequence identity to Neublastin, which in turn only shares 34-36% sequence identity with GDNF.<sup>7</sup> Thus, Artemin disclosed in Milbrandt is structurally distinct from GDNF disclosed in Yan.

Artemin and GDNF also possess differing biological activity. As is summarized in the specification at page 2, lines 6-7, Artemin/Neublastin exhibits high affinity for GDNF family receptor  $\alpha$  3 (GFR $\alpha$ 3). GDNF, on the other hand, does not bind to GFR $\alpha$ 3, but rather binds to GDNF family receptor  $\alpha$  1 (GFR $\alpha$ 1). The specification at page 55, lines 19-21 highlights the functional difference between Neublastin and GDNF as follows:

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<sup>2</sup> Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, published in the Federal Register, Vol. 72, No. 195, pages 57526-57535..

<sup>3</sup> *Id.* at 57528.

<sup>4</sup> See *Id.* at 57528, citing KSR, 82 USPQ2d at 1397.

<sup>5</sup> *Id.*

<sup>6</sup> See Office Action at page 9.

<sup>7</sup> See Table 4 in the Specification at page 50.

[N]eublastin binds to GFR $\alpha$ 3 but not to GFR $\alpha$ 1. This behavior clearly distinguishes neublastin from GDNF; as shown in FIG. 11, GDNF binds to GFR $\alpha$ 1 but not to GFR $\alpha$ 3.

Thus, as is clear from the evidence of the specification, the protein Artemin/Neublastin disclosed in Milbrandt is functionally distinct from GDNF disclosed in Yan. The claims have been amended to recite that the Neublastin polypeptides of the claims bind to GFR $\alpha$ 3 with greater specificity as compared to GFR $\alpha$ 1. Thus, the claims have been amended to recite the structural and functional properties of Neublastin polypeptides that distinguishes these growth factors from other growth factors such as GDNF.

Taken together, Artemin/Neublastin is structurally and functionally distinct from GDNF. Accordingly, this does not create a scenario where a person of ordinary skill in the art could easily substitute one element of the prior art for another. The Office Action relies on the general teachings in Yan and Milbrandt that identify Artemin/Neublastin and GDNF generally as neurotrophic growth factors. The Office Action, however, fails to consider the distinct modes of action by which these growth factor elicit their biological effect. Further, the Office Action fails to set forth a rationale as to why a person of ordinary skill in the art would expect two structurally and functionally distinct polypeptides operating through distinct receptor pathways to be obvious substitutions for one another. That Artemin/Neublastin and GDNF are generally known in the art as neurotrophic growth factors can not support a conclusion that the claims would have been obvious to one of ordinary skill in the art.

Furthermore, as is explained by the Federal Circuit, the motivation to combine is part of the discussion in determining the scope and content of the prior art.<sup>8</sup> Thus, where all claim limitations are found in a number of references, the factfinder must determine "[w]hat the prior art teaches... and whether it motivates a combination of teachings from different references".<sup>9</sup> Here, Milbrandt fails to disclose a method of using

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<sup>8</sup> DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co., 464 F.3d 1356, 1360, 80 USPQ2d 1641, 1645 (Fed. Cir. 2006); *citing* SIBIA Neurosciences, Inc. v. Cadus Pharma, Corp., 225 F.3d 1349, 1356 (Fed. Cir. 2000).

<sup>9</sup> *Id.* *citing* In re Fulton, 391 F.3d 1195, 1199-1200 (Fed. Cir. 2004).

Artemin/Neublastin for the treatment of an eye disorder such as macular degeneration, retinitis pigmentosa, or glaucoma. Nowhere in Milbrandt is it even taught that Artemin/Neublastin is expressed in the retina. Thus, there is no suggestion in Milbrandt that Artemin/Neublastin may be used in the manner now claimed. Yan discloses use of GDNF, which as above, is a structurally different protein and produces its biological effect through a different biological mechanism. A person of ordinary skill in the art would appreciate these differences and would not have been motivated to combine the teachings of Yan and Milbrandt to arrive at the present invention. Because of the structural and functional differences between Artemin and GDNF, a person of ordinary skill in the art would not “be able to fit the teachings of multiple patents together like pieces of a puzzle.”<sup>10</sup>

Moreover, Applicants respectfully submit that this rejection is inapposite claims 91 and 92. To establish *prima facie* obviousness of a claimed invention, all claim limitations must be taught or suggested by the prior art.<sup>11</sup> The primary reference of Yan is fatally defective in this regard. First, Yan does not disclose the instantly claimed Neublastin polypeptides. Nor does it disclose treatment of retinitis pigmentosa or macular degeneration with any protein. The secondary reference of Milbrandt also does not disclose the treatment of retinitis pigmentosa or macular degeneration with the recited Neublastin polypeptides. Milbrandt therefore does not cure the deficiencies of the primary reference. Nor does the Office Action rely on Milbrandt to cure such deficiencies. This forces the conclusion that the combination of the cited references would not teach all elements of claims 91 and 92, and therefore does not and can not render obvious the present claims.

In view of the above, Applicants respectfully submit that the Office Action fails to set forth a *prima facie* case of obviousness. Accordingly, Applicants request withdrawal of this rejection.

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<sup>10</sup> KSR, 82 USPQ2d at 1397.

<sup>11</sup> M.P.E.P. § 2143.03.

**CONCLUSION**

An indication of allowance of all claims is respectfully solicited. Early notification of a favorable consideration is respectfully requested. In the event any issues remain, Applicant would appreciate the courtesy of a telephone call to their counsel to resolve such issues and place all claims in condition for allowance.

Respectfully submitted,

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